CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-644

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: **21-644**	Submission Date(s): 05/06/03
Brand Name	Clobex Shampoo™ 0.05%
Generic Name	Clobetasol Propionate, 0.05%
Reviewer	Chandra S. Chaurasia, Ph. D.
Team Leader	E. Dennis Bashaw, Pharm.D.
OCPB Division	DPE III (HFD-880)
OND division	ODE V (HFD-540)
Sponsor	Galderma Laboratories, L. P., Fort Worth, TX 76177
Relevant IND(s)	60,934
Submission Type; Code	New formulation
Formulation; Strength(s)	Shampoo 0.05%
Indication	Treatment of moderate to severe [redacted] scalp psoriasis

1. EXECUTIVE SUMMARY

Clobex Shampoo™ contains the active compound clobetasol propionate 0.05% for topical dermatologic use. Clobetasol is a synthetic corticosteroid with a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity. In the US, clobetasol is commercially available in 0.05% strength as various topical dosage forms such as, Temovate® Cream, Temovate® Ointment, Temovate® Gel, Temovate® Scalp Application and Olux® Foam. Temovate Cream is marketed under the name of Dermoval® in France. In addition, clobetasol has been recently approved as 0.05% lotion (Clobex Lotion, NDA 21-535) manufactured by Galderma Labs, the Sponsor of this NDA.

In this submission, the Sponsor pursues the approval of a shampoo dosage form of clobetasol propionate, 0.05% for the relief of [redacted] of moderate to severe forms of scalp psoriasis. As stated by the Sponsor, the proposed Clobex Shampoo offers the convenience of once daily short contact dosing which is an advantage compared to twice daily dosing of the Temovate Scalp Application, 0.05% and Olux Foam, 0.05% products available in the US to treat scalp psoriasis.

To support the NDA the Sponsor has submitted the following 4 studies to evaluate the bioavailability of Clobetasol Propionate Shampoo, 0.05%:

- Vasoconstriction Assay (CG.03.SRE.2618): Comparing Clobetasol Propionate Shampoo with three commercialized products and its vehicle.
- Ocular Safety and HPA axis suppression study (CG.03.SRE.2620): On both scalp psoriasis and scalp seborrheic dermatitis subjects.
- HPA axis suppression study (RD.06.SRE.18070): In adolescents 12-17 years with scalp psoriasis.
- Comparison of in vitro liberation-penetration study of Clobetasol Propionate applied as two different formulations onto human skin (CG.03.SRE.4651)

Based on the reported results of vasoconstrictor study, Clobex Shampoo exhibits Class I medium-to-high vasoconstrictor potency compared to Temovate Cream and Temovate Scalp Application.

The HPA axis suppression study (CG.03.SRE.2620) was conducted in Europe in scalp psoriasis and scalp seborrheic dermatitis adult subjects. The study design in general was flawed because of the following reasons:

- Many subjects exhibited very high levels (> 18 μg/dL) of cortisol at the screening. A doubling of the cortisol levels post-stimulation following Cosyntropin administration would have been unrealistic in these subjects. Thus, these subjects should not have been enrolled in the study.
- The study subjects were evaluated weekly with Cosyntropin stimulation on weeks 1, 2, 3 and 4. Such frequent exposure with Cosyntropin is likely to manifest higher plasma cortisol levels at the end of the desired 4-week period leading to a false negative interpretation (i.e., no HPA axis suppression).

Based on the reported results of HPA axis trials, there appears to be a marked incidence of HPA axis suppression with the Clobex Shampoo both in the adult and adolescent populations. In addition, as noted above the HPA axis suppression study conducted in Europe was erroneous. The reviewer, therefore, recommends that the Sponsor addresses this concern by conducting HPA axis analysis using an appropriate study design with adequate number of subjects.

1.1. RECOMMENDATIONS

From a Biopharmaceutics perspective the firm has provided evidence of systemic availability of the test Clobex Propionate Shampoo using HPA suppression as a pharmacodynamic end point. The Study No. SRE2610 conducted in Europe in adult patients is flawed, and no meaningful results can be interpreted from it. Based on the results of HPA axis trial in adolescents (12-17 years, Study No. SRE 18070), use of Clobex Shampoo is clearly associated with a significant incidence of HPA suppression as 5 out of 12 (42%) evaluable subjects exhibit HPA axis suppression in this population. It is also noted that the number of subjects (N=13) used in Study 18070 was rather small for this type of study. While the bioavailability of clobetasol has been determined via indirect methods (i.e., HPA axis testing), from a clinical pharmacology perspective, the safety issues raised by the suppression of the HPA axis in adolescents brings up a significant concern regarding the adult population that needs to be addressed by the Sponsor. The reviewer, therefore, recommends that the Sponsor conducts HPA axis studies using an appropriate study design with adequate number of subjects both in the adult and adolescent populations for comparative safety purpose.

_____ Date: _____

Chandra S. Chaurasia, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

2. TABLE OF CONTENTS

SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Clobetasol Propionate is a topical corticosteroid, and as such classical in vivo pharmacokinetic studies involving plasma drug measurement are not possible due to minimal percutaneous absorption and limit of detection issues. For a topical corticosteroid, evidence of Hypothalamus-Pituitary-Adrenal (HPA) axis suppression is used as a surrogate for in vivo bioavailability evaluation

In the current submission, the biopharmaceutic/bioavailability evaluation of the shampoo is based on the following comparative studies:

Vasoconstrictor Assay Comparison in Healthy Subjects

Study 1.CG.03. SRE.2618: Vasoconstriction Assay Comparing Clobetasol Propionate Shampoo with Three Commercialized Products (Temovate Scalp Application, 0.05%, Temovate Cream, 0.05% and Diprolene Cream, 0.05%), and its vehicle.

Adrenal Suppression Studies in Clinical Subjects

1. **Study No. 1.CG.03.SRE.2620**: Ocular Safety and HPA Axis Suppression Potential of Clobetasol Propionate Shampoo, 0.05% on both scalp psoriasis and scalp seborrheic dermatitis subjects.
2. **Study No. RD.06.SRE.18070**: HPA Axis Suppression Potential of Clobetasol Propionate Shampoo, 0.05% in adolescents 12-17 years with scalp psoriasis.

In Vitro Study

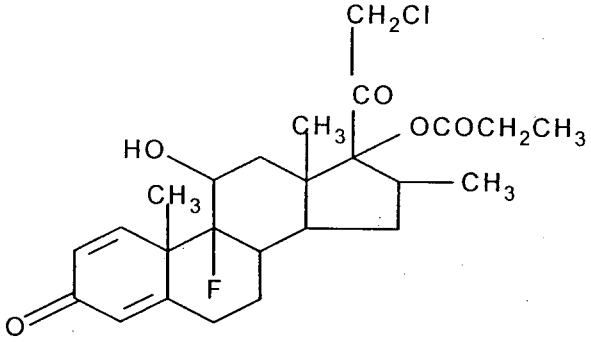
Study No. CG.03. SRE.4651: Comparison of the in vitro liberation-penetration of clobetasol propionate applied as two different formulations (Clobetasol Propionate Shampoo, 0.05% vs. Temovate Scalp Application) onto human skin.

The above studies were reviewed in detail. The findings are summarized in the review described in the following sections.

4. QUESTION-BASED REVIEW

4.1. General Attributes

What are the highlights of the physicochemical properties of clobetasol propionate?
Chemically, clobetasol propionate is 11(beta),16(beta))-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy) pregna-1,4-diene-3,20-dione, and it has the following structural formula:



Clobetasol propionate has the empirical formula $C_{25}H_{32}ClFO_5$ and a molecular weight of —. It is a white to cream-colored crystalline powder insoluble in water.

What are the properties of the formulation of the drug product?
The active ingredient is dissolved ——— shampoo dosage form consisting of inactive ingredients as indicated in the drug product formulation in the following Table:

Components and Composition of Clobetasol Propionate Shampoo, 0.05%

	Percent (w/w)	Per Gram
Clobetasol propionate, USP	0.05	—
Alcohol (Ethanol —, USP	[redacted]	
Coco-betaine —		
Sodium laureth sulfate —		
Polyquaternium-10		
Sodium citrate dehydrate, USP		
Citric acid monohydrate, USP		
Purified water, USP	62.11	—

The above Lots were used in the two Phase II HPA axis studies RD.06.SRE.18070 and CG.03.SRE.2618 as well as in two Phase III clinical studies RD.06.SPR.18075 and RD.06.SPR.18076.

What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of clobetasol propionate shampoo, 0.05%?
Indication:
Clobetasol Propionate Shampoo, 0.05% is indicated for ——— moderate to severe form of scalp psoriasis.

Dosage and Route of Administration:
Per the Sponsor's proposed labeling, Clobex Shampoo should be applied to the affected areas of the scalp once a day. The product should be applied on dry scalp and left in place for 15 minutes before lathering and rinsing. Clobex Shampoo is a medium-to-high potent topical corticosteroid

formulation. Treatment should be limited to 4 consecutive weeks. Clobex Shampoo should not be used with occlusive dressing unless directed by a physician.

Mechanism of Action:
Like other topical corticosteroids, Clobetasol Propionate Shampoo, 0.05% has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids in general is unclear. However, corticosteroids are thought to act by induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

4.2. General Clinical Pharmacology

What studies have been conducted for biopharmaceutic/bioavailability evaluation of the drug product? What are the outcomes of these studies?

- Clobetasol Propionate 0.05% Shampoo is a topical corticosteroid and as such classical in vivo pharmacokinetic studies involving plasma drug measurement are not possible due to minimal percutaneous absorption and limit of detection issues. For a topical corticosteroid evidence of Hypothalamus-Pituitary-Adrenal (HPA) axis suppression is used as a surrogate for in vivo bioavailability. The firm has submitted two, studies RD.06.SRE.18070 and CG.03.SRE.2618 with the results of HPA axis suppression in scalp seborrheic dermatitis and scalp psoriasis in adults and in scalp psoriasis in adolescent populations.
- Additionally, to establish the potency of Clobex Shampoo, the firm conducted vasoconstrictor study 1.CG.03.SPR.2618 comparing the Clobetasol Propionate Shampoo with Three Commercialized Products (Temovate Scalp Application, 0.05%, Temovate Cream, 0.05% and Diprolene Cream, 0.05%), and its vehicle.

Results of HPA Axis Suppression Studies: Based on the reported results, there appears to be a considerable HPA axis suppression following 4 weeks of topical application of the Clobetasol Propionate Shampoo both in the adults (more than 85% or 12 out of 14 evaluable subjects) and adolescents (more than 46% or 6 out of 13 evaluable subjects). The results are summarized in the Table below. Details of the HPA axis suppression studies are provided in **Section 6.2: Appendix II. 6.2.3 and 6.2.4** of the review.

HPA Axis Suppression following 2 and/or 4 weeks application of Clobetasol Propionate Shampoo in Adult and Adolescents Scalp Seborrheic and Psoriasis Patients

Treatments	HPA Axis Suppression (n, %), N*	
Study No. SRE2620 (Scalp Seborrheic Dermatitis) in Adults Ex-US Study		
	Week 2	**Week 4**
Clobetasol Propionate Shampoo	12 (92%), N=12	11 (85%), N=13
Dermoval (Clobetasol Propionate Gel, 0.05%) Ex-US product	12 (92%), N=12	10 (77%), N=13
Study No. SRE2620 (Scalp Psoriasis) in Adults Ex-US Study		
Clobetasol Propionate Shampoo	9 (64%), N=14	12 (86%), N=14
Dermoval (Clobetasol Propionate Gel, 0.05%) Ex-US product	10 (83%), N=12	10 (83%), N=12
Study No. SRE18070(Scalp Psoriasis) in Adolescents		
Clobetasol Propionate Shampoo	N/A	6 (46%), N=13

**n = subjects with HPA suppression, N = total number of subjects completing the study at the end of the week.*

Results of Vasoconstriction Study

Results of Vasoconstrictor Studies: Based on the vasoconstrictor assay, the Clobetasol Propionate Shampoo 0.05% is inferior to two known formulations containing the same active ingredient at the same concentrations (Temovate Cream and Temovate Scalp Application) in its ability to cause vasoconstriction. Both Temovate cream and scalp application are Class I super potent steroids. Clobetasol propionate shampoo does produce more vasoconstriction than Diprolene cream, a Class 1 low potency steroid. Thus, the vasoconstrictor potency of Clobetasol propionate shampoo 0.05% is expected to be in the range of mid-to-high potent corticosteroid. However, because of both the small number of comparators and their wide differential in vasoconstrictor potency relative to each other, the test is unable to differentiate between high potent and super-high potent agents. Because of this and the observed HPA suppressive action of the Clobetasol Propionate Shampoo 0.05%, we decided to classify this formulation belonging to the super-high potent class. Details of the vasoconstrictor study are provided in Section 6.2: Appendix II. 6.2.2.

Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters?

Plasma samples were analyzed by validated HPLC- ——— method for the HPA axis studies SRE.2620 and SRE 18070 (see Section 4.6) to determine the concentrations of clobetasol propionate following topical administration. No quantifiable amounts of clobetasol were found in any of the 56 samples analyzed at a detection limit of ———

What are the basic pharmacokinetic parameters of clobetasol propionate shampoo (ADME)?

Since the systemic plasma levels of clobetasol after topical administration are below the limit of quantitation ——— , a basic PK profile of the drug product could not be obtained.

4.3. Intrinsic Factors: Age, Sex, Race, Weight, Height and Disease States.

Clobetasol propionate shampoo 0.05% is for topical administration. Considering the undetectable plasma concentrations of clobetasol propionate after topical administration, PK studies involving intrinsic factors (e.g., gender or age, renal and hepatic impairments) is not possible at this time.

4.4. Extrinsic Factors: Drugs, Diets and Smoking

Again, considering the undetectable plasma concentrations of clobetasol propionate after topical administration, evaluation of the effect of any extrinsic factors on clobetasol propionate shampoo, 0.05% is not possible at this time.

4.5 General Biopharmaceutics

Are there any differences between clinical and to-be-marked formulations?

All batches/lots and sub lots (662.066//2F1/2F3/BLJ-1) utilized in clinical and human biopharmaceutic studies to support this application were made with the to-be-marketed formula.

Are there any in vitro data for clobetasol propionate 0.05% shampoo?

Clobex Shampoo was evaluated by comparing its in vitro liberation-penetration of clobetasol propionate to a 0.05% commercial formulation Temovate Scalp Application under similar application conditions. The results of this in vitro study demonstrated a similar percutaneous penetration of the clobetasol propionate from Clobex Shampoo and Temovate Scalp Application when left on the skin for the same time. The study is summarized in details in Appendix II.6.2.1.

4.6. Analytical

What bioanalytical methods are used to assess the amount of clobetasol propionate in plasma and for in vitro analyses? Have the analytical methods been fully validated?

Plasma Samples: Study No. 1.CG.03.SRE.2620 and Study No. RD.06.SRE.18070. The analysis of the human plasma samples to determine the concentrations of clobetasol propionate was carried out in the Bioanalysis Laboratory of Galderma Research Development, [redacted] France using a High Pressure Liquid Chromatography- [redacted] (HPLC- [redacted] method described in the validation report CG.03.VAL.4288.S01.

Summary of Analytical Method Validation:
Internal Standard: Clobetasol butyrate
Linearity Range: [redacted]
Lower Limit of Quantitation: [redacted]
Limit of Detection: [redacted]
Accuracy: [redacted] at QC samples 0.5, 1.0 and 5.0 ng/mL (for Study No. RD.06.SPR.18070)
[redacted] at QC samples 0.5, 1.0 and 5.0 ng/mL (for Study No. CG.03 SPR 2620) except one sample that exhibited a [redacted] error probably resulting from an analytical anomaly.
Precision: [redacted] at QC samples 0.5, 1.0 and 5.0 ng/mL
Specificity: Good. No degradation of clobetasol propionate was observed during the whole sample processing.
Long-term [redacted] Testing in Human Plasma: Good for at least [redacted]

Results: No quantifiable amounts of clobetasol propionate were found in any of 58 samples (45 plasma samples in Study 1.CG.03.SPR.2620 and 11 plasma and 2 blood samples in Study RD.06.SPR.18070) analyzed.

In Vitro Liberation-penetration Samples: The analysis of clobetasol in in vitro samples was accomplished by use of a High Pressure Liquid Chromatography-Mass Spectrometry (HPLC-MS) method described in the validation report CG.03.VAL.4248. The method has been validated for the concentration range of [redacted]

Summary of Analytical Method Validation:
Internal Standard: [redacted]
Linearity Range: [redacted]
Lower Limit of Quantitation: [redacted]
Accuracy: Better than [redacted] at QC samples 20, 60 and 250 ng/mL
Precision: Better than [redacted] at QC samples 20, 60 and 250 ng/mL
Specificity: Good. No degradation of clobetasol propionate was observed during the whole sample processing and after [redacted] at a temperature of [redacted]

Are analytical methods sensitive enough to determine the extent of clobetasol propionate absorption after topical application?

The analytical method used in the current studies had a detection limit [redacted]. At this level of sensitivity, no clobetasol propionate could be detected in the plasma samples following clobetasol propionate 0.05% shampoo topical administration.

4.7. Pharmacokinetic Data:

There are no PK data as no quantifiable amounts of clobetasol propionate were found in any of the 54 plasma samples analyzed based on the results from Report Nos. 1.CG.03.SPR.2620 and Study No. RD.06.SPR.18070.

5. LABELING RECOMMENDATIONS

Recommendations for changes to the proposed labeling are provided below (only affected sections related to clinical pharmacology are listed). The suggested additions and deletions in the text are indicated by ***bold italics*** and ~~red strikethrough~~ styles, respectively.

CLINICAL PHARMACOLOGY:

Like other topical corticosteroids, **CLOBEX™ Shampoo** has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier and occlusion ———— ————. Topical corticosteroids can be absorbed from normal intact skin, while inflammation and/or other disease processes in the skin may increase percutaneous absorption.

———————————————————————————

Due to the fact that circulating levels ***of corticosteroids are usually below the limit of detection following application, there are no human data regarding the pharmacokinetics of topical corticosteroids. In such cases pharmacodynamic end points, including both hypothalamic-pituitary-adrenal (HPA) axis testing and topical vasoconstriction, are used as surrogates in the assessments of systemic exposure and relative potency, respectively*** ————————————————

[ ]

In studies evaluating the potential for hypothalamic-pituitary-adrenal (HPA) axis suppression, use of CLOBEX™ (clobetasol propionate) Shampoo, 0.05%, resulted in demonstrable HPA axis suppression in 5 out of 12 (42%) adolescent patients (See PRECAUTIONS).

Studies performed with **CLOBEX™ Shampoo** indicate that it is in the superhigh range of potency as compared with other topical corticosteroids.

CLOBEX™ Shampoo is in the super-high range of potency in vasoconstrictor studies.

PRECAUTIONS:

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia,

and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Conditions which increase systemic absorption include the application of the more potent corticosteroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

1 page(s) of draft labeling has been removed from this portion of the review.

6. APPENDIX

6.1. Appendix I: SPONSORED PROPOSED LABELING (REVISED BY THE SPONSOR AS OF MARCH, 2003)

LABELING (DRAFT)

0.5 fl.oz. (15 ML) Physician sample (bottle) label

Principal Display Panel

NDC xxxx-xxxx-xx
Rx only
CLOBEX™ (clobetasol propionate) Shampoo, 0.05%

0.5 FL.OZ. (15 mL)
SAMPLE, NOT FOR SALE
Marketed by:
GALDERMA Laboratories, L.P.
Fort Worth, Texas 76177 USA

Information Panel

For External Use Only. Not for Ophthalmic Use.

Storage: Keep tightly closed. Store at controlled room temperature 68°F to 77°F (20°C - 25°C).

Usual dosage: See package insert for complete prescribing information.

Each mL contains: Active: clobetasol propionate, 0.05%. ——— alcohol, —— citric acid monohydrate; coco-betaine; polyquaternium-10; purified water; sodium citrate dihydrate and sodium laureth sulfate.
See Lot No. and Exp. Date on bottom of bottle.
(Part Number)
4 fl.oz. (118 ML) TRADE SIZE PRIMARY CONTAINER (bottle) label

Principal Display Panel
NDC xxxx-xxxx-xx
Rx only

CLOBEX™ (clobetasol propionate) Shampoo, 0.05%
4 FL.OZ. (118 mL)

Information Panel

For External Use Only. Not for Ophthalmic Use.

Usual dosage: Apply to affected areas of the scalp once daily. Apply on dry scalp and leave in place for 15 minutes before lathering and rinsing. See package insert for complete prescribing information.

Each mL contains: Active: clobetasol propionate, 0.05%. [illegible]: alcohol, [illegible] citric acid monohydrate; coco-betaine; polyquaternium-10; purified water; sodium citrate dihydrate and sodium laureth sulfate.

Storage: Keep tightly closed. Store at controlled room temperature 68°F to 77°F (20°C - 25°C).

Lot No. and Exp. Date.

Marketed by:
GALDERMA Laboratories, L.P.
Fort Worth, Texas 76177 USA
Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215 USA
(Part Number)
4 fl.oz. (118 ML) TRADE SIZE SECONDARY CONTAINER (CARTON BOX) label

FRONT AND BACK PANELS

NDC xxxx-xxxx-xx
Rx only

CLOBEX™ (clobetasol propionate) Shampoo, 0.05%
4 FL.OZ. (118 mL)

GALDERMA (Logo)

LATERAL PANELS

For External Use Only.
Not for Ophthalmic Use.

Usual dosage: Apply to affected areas of the scalp once daily. Apply on dry scalp and leave in place for 15 minutes before lathering and rinsing. See package insert for complete prescribing information.

Each mL contains: Active: clobetasol propionate, 0.05%. [illegible]: alcohol, [illegible] citric acid monohydrate; coco-betaine; polyquaternium-10; purified water; sodium citrate dihydrate and sodium laureth sulfate.

Storage: Keep tightly closed. Store at controlled room temperature 68°F to 77°F (20°C - 25°C).

Marketed by:
GALDERMA Laboratories, L.P.
Fort Worth, Texas 76177 USA
Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215 USA
(Part Number)

TOP PANEL

CLOBEX™ (clobetasol propionate) Shampoo, 0.05%
4 FL.OZ. (118 mL)

BOTTOM PANEL

Lot No.:
Exp. Date:

PHYSICIAN PACKAGE INSERT

CLOBEX™ (clobetasol propionate) Shampoo, 0.05%

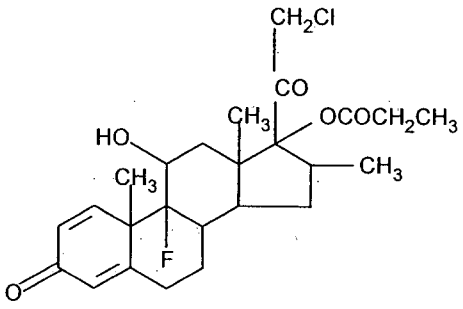
Rx Only
For External Use Only
Not for Ophthalmic Use

DESCRIPTION:

CLOBEX™ (clobetasol propionate) Shampoo contains clobetasol propionate, USP, a synthetic fluorinated corticosteroid, for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents.

The chemical name of clobetasol propionate is 21-Chloro-9-fluoro-11β, 17-dihydroxy-16β-methylpregna-1, 4-diene-3, 20-dione 17-propionate.

It has the following structural formula:



Clobetasol propionate

Clobetasol propionate has a molecular weight of 466.97 (CAS Registry Number 25122-46-7). The molecular formula is $C_{25}H_{32}ClFO_5$. Clobetasol propionate is a white to practically white crystalline, odorless powder insoluble in water.

Each mL of CLOBEX™ Shampoo contains clobetasol propionate, 0.05%, — , in a shampoo base consisting of alcohol, — citric acid monohydrate; coco-betaine; polyquaternium-10; purified water; sodium citrate dihydrate and sodium laureth sulfate.

CLINICAL PHARMACOLOGY:

Like other topical corticosteroids, **CLOBEX™ Shampoo** has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier . Topical corticosteroids can be absorbed from normal intact skin while inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Due to the fact that circulating levels are below the level of detection,

CLINICAL STUDIES:

The safety and efficacy of **CLOBEX™ Shampoo** has been in two clinical trials involving 290 patients moderate to severe scalp psoriasis.

INDICATIONS AND USAGE:

CLOBEX™ Shampoo is a superhigh potent topical corticosteroid formulation of moderate to severe forms of scalp psoriasis. Treatment should be limited to 4 consecutive weeks because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Patients should be instructed to use **CLOBEX™ Shampoo** for the minimum time period necessary to achieve the desired results (see **PRECAUTIONS**).

CONTRAINDICATIONS:

CLOBEX™ Shampoo is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation.

PRECAUTIONS:

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Conditions which increase systemic absorption include the application of the more potent corticosteroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. (See **PRECAUTIONS - Pediatric Use**).

If irritation develops, **CLOBEX™ Shampoo** should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noting a clinical exacerbation, as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.
In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, use of **CLOBEX™ Shampoo** should be discontinued until the infection has been adequately controlled.

Although **CLOBEX™ Shampoo** is intended for the topical treatment of moderate to severe scalp psoriasis, it should be noted that certain areas of the body, such as the face, groin, and axillae, are more prone to atrophic changes than other areas of the body following treatment with corticosteroids. **CLOBEX™ Shampoo** should not be used on the groin or axillae. Avoid any contact of the drug product with ——— eyes and lips. In case of contact, rinse thoroughly with water all parts of the body that came in contact with the shampoo.

Information for patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. It is for external use only. Avoid contact with the eyes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The scalp area should not be covered while the medication is on the scalp (e.g., shower cap, bathing cap) so as to be occlusive unless directed by the physician.
4. Patients should report ——— any signs of local adverse reactions.
5. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 4 weeks, contact the physician.
6. Patients should wash their hands after applying the medication.
7. Patients should inform their physician(s) that they are using **CLOBEX™ Shampoo** if surgery is contemplated.

Laboratory tests: The ——— may be helpful in evaluating patients for HPA axis suppression:

[ ]

Carcinogenesis, mutagenesis, and impairment of fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

Nursing mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when **CLOBEX™ Shampoo** is administered to a nursing woman.

Pediatric

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence

of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric use:

ADVERSE REACTIONS:

In clinical trials with **CLOBEX™ Shampoo**, the following adverse reactions have been reported: burning/stinging, pruritus, edema, folliculitis, acne, dry skin, irritant dermatitis, alopecia, urticaria, skin atrophy and telangiectasia.

The following additional local adverse reactions have been reported infrequently with other topical corticosteroids, and they may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria.

Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

OVERDOSAGE:

Topically applied, **CLOBEX™ Shampoo** can be absorbed in sufficient amounts to produce systemic effects (See **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION:

CLOBEX™ Shampoo should be applied scalp once a day. and left in place for 15 minutes before lathering and rinsing.

Move the hair away from the scalp so that one of the affected areas is exposed. Position the bottle over the lesion. Apply a small amount of the shampoo directly onto the lesion, letting the product naturally flow from the bottle (gently squeeze the bottle), avoiding any contact of the product with the facial skin, eyes or lips. In case of contact, rinse thoroughly with water. Spread the product so that the entire lesion is covered with a thin uniform film. Massage gently into the lesion and repeat for additional lesion(s). Wash your hands after applying **CLOBEX™ Shampoo.**

Leave the shampoo in place for 15 minutes. Add water, lather and rinse thoroughly all parts of the scalp and body that came in contact with the shampoo (e.g., hands, face, neck and shoulders). Although no additional shampoo is necessary to cleanse your hair, you may use a non-medicated shampoo if desired.

. If no improvement is seen within 4 weeks, reassessment of diagnosis may be necessary.

CLOBEX™ Shampoo should not be used with occlusive dressings unless directed by a physician.

HOW SUPPLIED:

CLOBEX™ Shampoo is supplied in 4 fl.oz. (118 mL) bottles.
NDC xxxx-xxxx-xx
Storage: Keep tightly closed. Store at controlled room temperature 68°F to 77°F (20°C - 25°C).

Marketed by:
GALDERMA Laboratories, L.P.
Fort Worth, Texas 76177 USA

Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215 USA

GALDERMA is a registered trademark.

Revised: March, 2003

PATIENT INFORMATION

For External Use Only
Not for Ophthalmic Use

CLOBEX™ (clobetasol propionate) Shampoo, 0.05%

Read — information with CLOBEX™ Shampoo. There may be new information. This does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about CLOBEX™ Shampoo?

What is CLOBEX™ Shampoo?

Who should not use CLOBEX™ Shampoo?
Do not use CLOBEX™ Shampoo if you are allergic to any of its ingredients.

CLOBEX™ Shampoo is not recommended for use _____ years of age.

What should I tell my doctor before using CLOBEX™ Shampoo?
If you are pregnant, think you are pregnant, plan to be pregnant,

If you think you have an infection on your scalp,

Tell your doctor about all the other medicines and skin products you use, including prescription and non-prescription medicines, supplements.

How should I use CLOBEX™ Shampoo?

- Apply CLOBEX™ Shampoo on affected areas of the scalp once a day.

What should I avoid while using CLOBEX™ Shampoo?

What should I do if I miss an application of CLOBEX™ Shampoo?
If you forget to apply CLOBEX™ Shampoo at the scheduled time, use it as soon as you remember, and then go back to your regular schedule. If you remember at the time of your next application, apply only one dose and continue with your regular schedule. If you miss several doses, tell your doctor.

What are the possible side effects of CLOBEX™ Shampoo?

1 page(s) of draft labeling has been removed from this portion of the review.

6.2. Appendix II: Individual Study Reviews

6.2.1. In Vitro Study: Report No. 1. CG.03.SRE.4651: Comparison of the In Vitro Liberation-Penetration of Clobetasol Propionate Applied as Two Different Formulations onto Human Skin.

Objectives:

To evaluate the in vitro liberation [redacted] shampoo with and without washing the skin surface after topical application (use conditions) and secondly to compare the in vitro liberation-penetration of [redacted] from Clobex shampoo to one of a 0.05% commercial formulation Temovate Scalp Application in the same application conditions.

Study Site: Galderma Research and Development, 635 Route des Lucioles B.P. 87-06902 Sophia Antipolis CEDEX, France

Investigational Product: Clobex Shampoo containing 0.05% w/w [redacted] Formula/batch No. 662.066/2F1, Galderma Laboratories

Comparator Products: Temovate® Scalp Application containing 0.05% w/w [redacted] Batch No. 6L223

Method: Described in detail in NDA 21-644, Vol. 15. Item 6, pp. 8491. Briefly, human abdominal, crureus and groin full thickness skin removed during surgical procedures (from 6 different female donors) was used in all experiments. The permeation study was conducted using [redacted] The skin samples were maintained [redacted] . Concentrations of clobetasol propionate were measured using a validated HPLC-MS method. The limit of detection was [redacted]

The statistical analysis were performed in the epidermis, dermis and fluid receptor samples for the two formulations (described in detail in NDA 21-644, Vol. 15, Item 6, pp. 86 and 89).

Results and Conclusions:

The individual clobetasol propionate levels obtained during the study in the compartments (receptor fluid, epidermis, dermis, and non absorbed surface excess) are given in the NDA 21-644, Item 6, Vol. 15, pp. 96-100. The mean values are reported in the following Table:

Clobetasol propionate levels (µg) for 1 cm^2 of skin application (Arithmetic mean values ± SEM, N=12)

	Clobex Shampoo, 0.05%	Clobex Shampoo, 0.05%	Temovate Scalp Application
Application Period	**15 min**	**16 hr**	**16 hr**
Real Applied Dose	4.42±0.08 µg	4.59±0.14 µg	4.55±0.14 µg
Recovery in surface excess and upper cell washing % of the applied dose	3.82±0.27 87%	2.54±0.29 55%	2.993±0.32 66%
Epidermis + Stratum % of applied dose	0.002*±0.05 0.1%*	0.81±0.25 19%	0.32±0.05 7.2%
Dermis: D % of applied dose	BLQ NA	BLQ NA	BLQ NA
Total Skin: E+D % of applied dose	0.002* 0.1%*	0.81±0.25 19%	0.32±0.05 7.2%
Collected fractions (0-16 h) + lower cell washing	0.001* 0.03%*	BLQ NA	BLQ NA
Total Skin + Collected Fractions% of applied dose	0.004±0.003 0.1%	0.81±0.25 19%	0.32±0.05 7.2%
Mass Balance % of applied dose	3.83±0.27 87%	3.35±0.20 73%	3.32±0.31 73%

**11 values out of 12 are BLQ (* [redacted]

For Clobex shampoo, the total cutaneous penetration (epidermis and dermis) varied from 0.004± 0.003 µg (0.1% of the applied dose) after 15 minutes of application to 0.81± 0.25 µg of the applied dose after 16 hours of application. The quantities of [redacted] recovered in the excess were significantly higher (32%, $p<0.05$) when the application period of Clobex shampoo reached to 16 hours.

The total cutaneous penetration (epidermis and dermis) varied from 0.81± 0.25 µg (19% of the applied dose) for Clobex shampoo to 0.32± 0.05 µg (7% of the applied dose) for Temovate Scalp Application after 16 hours. The mass balance evaluation indicated an average recovery of 73% for the two formulations. No significant difference was observed between the two formulations concerning all the variable analyzed.

The results of this in vitro study demonstrate 1) a similar percutaneous penetration of the clobetasol propionate from Clobex Shampoo and Temovate Scalp Application when left on the skin for the same time, and 2) considerably reduced amount of clobetasol propionate penetration with shorter application time (15 min) consistent with the intended use conditions.

6.2.2. Vasoconstrictor Study: Report 1.CG.03.SPR.2618: Vasoconstriction assay comparing clobetasol propionate shampoo with three commercialized products and its vehicle.

Objectives:
To evaluate the blanching capacity of clobetasol propionate shampoo, 0.05% in comparison to two known formulations containing the same active ingredient at the same concentration (Temovate® Cream and Scalp® Application – Glaxo Wellcome Laboratories) and to one formulation containing 0.05% betamethasone dipropionate (Diprolene® Cream – Schering-Plough Laboratories).

Study Site:	[redacted]
Study Periods:	Start: Dec 02, 1998; Completion: Dec 15, 1998.
Investigational Product:	Clobex Shampoo (Clobetasol Propionate 0.05% shampoo), Batch No. 662.066/2F1, Galderma Laboratories
Comparator Products:	Temovate® Cream (Clobetasol Propionate 0.05% Cream) Temovate® Scalp Application (Clobetasol Propionate 0.05%) Diprolene® Cream (Betamethasone Dipropionate 0.05% Cream) Clobetasol shampoo vehicle
Treatment Duration:	Pre-test: Application of Temovate Cream for 16 hours, visual scoring 2 hours after product removal. Test: Application of products for 15-minutes, visual scoring at 4, 6, 8, 10, 12, 14 and 24 hours after product removal.
Dose:	50 µL of each product under occlusive patches

Methods: The study was conducted as monocenter, investigator-blinded, active- and vehicle-controlled, randomized, intra-individual trial. Each formulation was applied on the forearm of 12 healthy subjects chosen after Stoughton pre-test (highest visual scores obtained two hours after removal of a 16-hour occlusive application of 50 mL of Temovate cream). During the test 50 mg of each formulation were applied as a 15-min occlusive patch-test onto the forearm skin of the subjects according to a pre-established randomization list. Baseline chromametric measurements were performed prior to the application of the product. The vasoconstriction evaluation was carried out on five treated sites and one untreated site, using visual scoring and chromametry at 4, 6, 8, 10, 12, 14 and 24 hours after removal of excess product.

Sixteen healthy male subjects (all White Caucasian) were screened for the study and 12 met the criteria for study inclusion. All 12 subjects completed the study. The mean age was 28.3 +/- 2.9 years (range 25-35 years. No treatment-related adverse events were reported. Study inclusion and exclusion criteria are described in Vol. 15, Item 6, pp. 211-212.

Visual Score:
Visual scoring was carried out by two different evaluators using the scale of 0-4 (0 corresponds to unmodified skin and 4 to blanching considered being maximum).

Chromametric Measurements:
The chromametric measurements were carried out with a ———— Chromameter. The evaluations were made by two independent investigators at 4, 6, 8, 10, 12, 14 and 24 hours after removal of the excess product. The measurements were expressed numerically by the values of the L* and a* parameters (detail given in Vol. 15, Item 6, page 218).

Statistical Methods:
The following variables were statistically analyzed:
For visual scoring, the average between both evaluators values was calculated and an AUC was calculated by the trapezoidal rule.
For the chromameter measurements, the parameter L* and a* were averaged between measurements per site and adjusted for baseline correction. An AUC was calculated for the application duration.

AUCs obtained were subjected to analysis of variance by parameters and types of application, to compare the formulation with Temovate and Diprolene and with the non treated zone using the contrast method and the least squared mean.

Visual scores and Chromametric measurements of L* and a* Parameters and the corresponding descriptive statistics are provided in Vol. 15, Item 6, pages 336-415. AUCs values for visual scores and colorimetric measurements are summarized below:

AUC Values: Visual Scores (LS Mean), Report No. 1.CG.03.SRE.2610

	No Treatment	Clobetasol Vehicle	Clobetasol Shampoo 0.05%	Diprolene Cream 0.05%	Temovate Cream 0.05%	Temovate Scalp Application 0.05%
AUC	0.7786	0.5885	9.7682	2.8620	22.4635	36.8984
p	0.0060	0.0077	.	0.0419	0.0003	0.0001

AUC Values: Chromameter Measurements (LS Mean), Report No. 1.CG.03.SRE.2610

	No Treatment	Clobetasol Vehicle	Clobetasol Shampoo 0.05%	Diprolene Cream 0.05%	Temovate Cream 0.05%	Temovate Scalp Application 0.05%
L* Parameter (LS Mean)						
AUC	8.54	7.32	22.64	11.78	34.92	61.97
p	0.0169	0.0804	.	0.2120	0.1588	0.0001
a* Parameter (LS Mean)						
AUC	7.74	4.37	-16.28	-5.75	-27.87	-30.28
p	0.0001	0.0003	.	0.0555	0.0357	0.0121

Comments on Results of Vasoconstriction Studies:

- The firm has conducted [redacted] bioassay to establish the vasoconstriction potency of Clobetasol propionate shampoo. However, from an NDA point of view, emphasis is to establish a relative potency in relation to a high and low potency corticosteroid, and thus a single point [redacted] assay would have been sufficient.
- For visual scoring, the vasoconstrictor activity of Clobex shampoo was significantly higher than those for the vehicle, untreated site and Diprolene Cream ($p<0.042$), but lower than those of Temovate Cream or Temovate Scalp Application ($p<0.0001$).
- For chromameter reading a* parameter, the vasoconstrictor activity of Clobex shampoo was about one-half lower that those of Temovate Scalp Application or Temovate Cream ($p < 0.036$) and about three times higher than that of the Diprolene Cream ($p = 0.056$).
- For chromameter reading L* parameter, Clobex shampoo vasoconstrictor activity was about one-third of the Temovate Scalp Application ($p= 0.0001$), however, there was no significant difference between the Clobex shampoo and Temovate Cream or Diprolene cream ($p>0.15$).

Conclusion on vasoconstrictor studies:
Based on the vasoconstrictor study, the Clobetasol Propionate Shampoo 0.05% is inferior to two known formulations containing the same active ingredient at the same concentrations (Temovate Cream and Temovate Scalp Application) in its ability to cause vasoconstriction. Both Temovate cream and scalp application are Class I super potent steroids. Clobetasol propionate shampoo does produce more vasoconstriction than Diprolene cream, a Class 1 low potency steroid. Thus, the vasoconstrictor potency of Clobetasol propionate shampoo 0.05% is expected to be in the range of mid-to-high potent corticosteroid. However, because of both the small number of comparators and their wide differential in vasoconstrictor potency relative to each other, the test is unable to differentiate between high potent and super-high potent agents. Because of this and the observed HPA suppressive action of the Clobetasol Propionate Shampoo 0.05%, we decided to classify this formulation belonging to the super-high potent class.

6.2.3. HPA Axis Suppression Study: Report CG.03.SRE.2620: Ocular Safety and HPA Axis Suppression Potential of Clobetasol Propionate Shampoo 0.05% - A Study on Both Scalp Psoriasis and Scalp Seborrheic Dermatitis Subjects

Objectives:
To evaluate the ophthalmological irritation potential and the HPA axis suppression potential of a Shampoo containing Clobetasol Propionate shampoo 0.05% in subjects with scalp psoriasis and scalp seborrheic dermatitis as compared to a marketed corticosteroid, Dermoval /Temovate gel 0.05%.
Study Site: [redacted]

Study Period: Start: May 31, 1999; Completion: Nov 22, 1999.

Investigational Product:	Clobetasol Propionate Shampoo 0.05%, Lot No. 662.066/2F3 (Galderma – Sophia Antipolis)
Comparator Products:	DermovalGel 0.05%
Dose:	
Investigational Product:	Twice a week for Scalp Seborrheic Dermatitis

	Once a day for Scalp Psoriasis
Comparator Product:	Once a day application for both Scalp Psoriasis and Scalp Seborrheic Dermatitis
Mode of Administration:	15 minute application on dry hair before rinsing
Duration of Treatment:	4 weeks

Methods: The study was conducted as a single center, randomized, investigator-masked, parallel group comparison involving 52 subjects (28 males and 24 females, all White, ages 18 to 56 years, mean age 47.4) with scalp seborrheic dermatitis (N=26, 13 males and 13 females) or scalp psoriasis (N=26, 15 males and 11 females) involving at least 25% of scalp surface. Specific inclusion/exclusion criteria were: Subjects with a TDSS (Total Dermatological Sum Score (i.e., sum of erythema, desquamation, plaque thickening for psoriasis and sum of erythema, loose and adherent desquamation for seborrheic dermatitis) of at least 3, with a normal ocular status, and a normal HPA axis function defined as an 8.00 am serum cortisol level of at least 10 mcg/dL before stimulation with Cosyntropin and a minimum cortisol increase of 8 mcg/dL 60 minute after stimulation with 0.25 mg of Cosyntropin administered by intravenous injection (detail criteria described in NDA 21-644, Vol. 1.16 page 447-448).

Qualified subjects were randomized to receive either clobetasol propionate shampoo, 0.05% applied twice a week for subjects with scalp seborrheic dermatitis and once a day for subjects with scalp psoriasis or Dermoval/Temovate gel 0.05% applied once daily for both populations for a period of 4 weeks. Dose could not exceed 40 g/week. The exact amount of Dermoval gel used per week by each subject was determined at the end of the study by weighing the returned package. In the case of test product, subjects were provided with 10 mL unit-dose vial. The maximum quantity used for psoriasis subjects could not exceed 70 mL/week* and that for scalp seborrheic dermatitis subjects was 20 mL*. The average dose per week (established considering that all the subjects applied the same amount of product for each application and by dividing the maximum estimate weight of each product by the number of week of treatment) is presented in the following table:

Extent of Exposure to the Study Medications

Diseases	Scalp seborrheic dermatitis group N=26		Scalp psoriasis group N=26	
Products	Clobetasol shampoo, N=13	Dermoval Gel, N=13	Clobetasol shampoo, N=14	Dermoval Gel, N=12
Average Dose (g) per week*	16.4	30.1	65	28

**As expressed in the NDA 21-644 page 00477 Item 6, Volume16. The reviewer assumes that 1 mL of the test and comparator products approximately equals 1 gm.*

Ophthalmologic exam by slit lamp examination, visual acuity and intra ocular pressure were monitored at inclusion visit, before Cosyntropin injection and at each visit.

Clobetasol plasma levels were assessed for all subjects at Week 4 (3±1 hours after the last drug application). Blood samples (about 10 mL) were collected, [redacted] The samples were analyzed by HPLC. [redacted] The method was validated between the range of [redacted] for clobetasol propionate with the limit of detection at [redacted] (Validation report No. 1.CG.03.42880).

Of the 52 subjects enrolled, four subjects discontinued treatment: Sub. no.1 and 24, clobetasol shampoo on week 1; and Sub. No. 20 and 49 Dermoval/Temovate gel on week 2. Out of the four subjects discontinued, three were due to adverse events unrelated to study medications and one was due to subject's request.

Subjects were evaluated at Screening, Baseline (14 days after inclusion), and at Weeks 1,2, 3, and 4. All subjects who received at least one dose of the study medication and have at least one post-baseline safety evaluation were included in the safety analysis.

Results: The results are summarized in the Tables below.

Table 1. Report SRE2620: Pre and Post-Stimulation Cortisol Levels: Clobetasol Propionate 0.05% Shampoo Treatment Group in Seborrheic Dermatitis Patients

Sub #	Cortisol levels (µg/dL)											
	INCLUSION			BASELINE (WEEK 0)			WEEK 2			WEEK 4		
	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff
1	26.7	37.5	10.8	20.8	35.2	14.4	22.4*	34.5*	12.1*	22.4*	34.5*	12.1*
2	12.0	25.9	13.9	15.0	28.3	13.3	**14.8**	**24.0****	9.2	21.3	31.2	9.9
5	18.7	26.4	7.7	18.8	23.8	5.0	23.2	33.9	10.7	17.1	23.8	6.7
7	20.1	31.1	11.0	15.4	26.9	11.5	**21.2**	**32.2****	11.0	**20.0**	**36.2****	16.2
8	21.9	33.5	11.6	22.4	38.5	16.1	**22.2**	**35.5****	13.3	19.6	27.0	7.4
11	23.1	37.3	14.2	26.6	37.2	10.6	**19.6**	**32.8****	13.2	**24.7**	**38.3****	13.6
14	21.1	33.8	12.7	11.0	22.0	11.0	21.9	24.8	2.9	**13.3**	**32.4**	19.1
17	16.4	26.4	10.0	13.6	25.6	12.0	**13.4**	**23.5****	10.1	21.7	28.3	6.6
18	16.5	31.7	15.2	16.9	32.8	15.9	**18.8**	**34.9****	16.1	**21.8**	**38.3****	16.5
22	14.6	26.6	12.0	18.3	27.1	8.8	20.2	26.9	6.7	**15.5**	**29.2****	13.7
23	24.4	32.7	8.3	18	33.3	15.2	**19.8**	**33.4****	13.6	**13.7**	**35.1**	21.4
24	23.6	32.8	9.2	21.8	32.3	10.5	14.5*	32.3*	17.8*	14.5*	32.3*	17.8*
26	20.2	28.2	8.0	21.7	32.1	11.4	22.6	30.2	7.6	20.1	29.8	9.7

***Week 1 only, values reflect LOCF (last observation carried forward)**
****post-stimulation value between 1.5-1.8 of the pre-stimulation value**

Table 2. Report SRE2620: Pre and Post-Stimulation Cortisol Levels: Dermoval Gel 0.05% Treatment Group in Seborrheic Dermatitis Patients

Sub #	Cortisol levels (µg/dL)											
	INCLUSION			BASELINE (WEEK 0)			WEEK 2			WEEK 4		
	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff
3	24.7	39.9	15.2	16.0	30.1	13.9	**15.7**	**31.3**	15.6	17.3	29.3	12.0
4	23.5	33.9	10.4	20.5	28.3	7.8	17.7	26.7	9.0	**17.7**	**37.4**	19.7
6	12.8	26.1	13.3	18.9	24.1	5.2	16.3	25.1	8.8	13.9	25.7	11.8
9	17.2	33.2	16.0	16.5	34.2	17.7	**6.5**	**31.3**	24.8	13.3	26.3	13.0
10	25.1	42.9	17.8	25.2	40.3	15.1	20.3	32.6	12.3	28.3	37.1	8.8
12	26.1	43.1	17.0	33.9	42.5	8.8	30.1	42.7	12.6	28.0	40.1	11.9
13	21.5	39.4	17.9	21.6	41.5	8.9	20.3	30.5	10.2	22.7	31.6	8.9
15	45.7	53.2	7.5	40.0	52.4	12.4	41.4	42.9	1.5	45.1	55.9	10.8
16	14.9	24.6	9.7	14.9	29.0	14.1	13.9	23.2	9.3	13.5	30.2	16.7
19	20.1	32.0	11.9	19.9	31.9	12.0	17.2	26.4	9.2	20.0	31.5	11.5
20	15.7	28.3	12.3	19.7	25.7	6.0	15.1*	26.9*	11.8	15.1*	26.9*	11.8
21	18.5	34.0	15.5	18.9	31.9	13.0	20.9	32.4	11.5	20.1	31.1	11.0
25	21.9	36.5	14.6	18.2	36.1	17.9	21.8	33.8	12.0	19.6	33.6	14.0

***Week 1 only, values reflect LOCF (last observation carried forward)**

Table 3. Report SRE2620: Pre and Post-Stimulation Cortisol Levels: Clobetasol Propionate 0.05% Shampoo Treatment Group in Psoriasis Patients.

Sub #	Cortisol levels (µg/dL)											
	INCLUSION			BASELINE (WEEK 0)			WEEK 2			WEEK 4		
	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff
32	35.2	43.5	8.3	36.1	50.5	14.4	42.7	53.5	10.8	41.4	46.8	5.4
33	24.7	32.7	8.0	28.7	46.4	17.7	28.1	34.5	6.4	27.5	43.3	15.8
35	17.0	30.0	13.0	24.1	26.5	2.4	20.3	26.9	6.6	25.2	29.4	4.2
38	14.9	25.7	10.8	14.9	25.1	10.2	14.9	32.1	17.2	10.8	23.4	12.6
39	16.6	26.3	9.7	15.5	27.2	11.7	14.7	36.2	21.5	19.9	28.9	9.0
41	19.3	30.5	11.2	16.7	25.5	8.8	16.3	29.9	13.6**	20.6	33.8**	13.2
44	42.5	50.1	7.6	33.7	50.1	16.4	48.3	57.3	9.0	49.6	63.8	14.2
46	18.1	27.8	9.7	16.7	27.2	10.5	14.4	31.5	17.1	17.9	27.0**	9.1
47	17.8	25.5	7.7	20.5	28.2	7.7	13.2	26.4	13.2	15.2	26.8**	11.6
50	22.3	30.5	8.2	23.1	30.3	7.2	23.2	32.5	9.3	23.5	31.1	7.6
51	25.8	36.9	11.1	23.7	32.4	8.7	32.3	32.7	0.4	22.2	30.5	8.3
54	22.9	31.9	9.0	18.0	33.7	15.7	17.3	34.4	17.1	22.1	31.8	9.7
55	17.4	28.3	10.9	12.9	28.8	15.9	11.2	29.5	18.3	10.6	26.4	15.8
56	22.8	36.6	13.8	13.6	34.7	21.1	22.0	38.7	16.7**	22.9	31.7	8.8

***Week 1 only, values reflect LOCF (last observation carried forward)**

Table 4. Report SRE2620: Pre and Post-Stimulation Cortisol Levels: Dermoval Gel 0.05% Treatment Group in Psoriasis Patients.

Sub #	Cortisol levels (µg/dL)											
	INCLUSION			BASELINE (WEEK 0)			WEEK 2			WEEK 4		
	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff	Pre-Stim	Post-Stim	Diff
31	23.5	42.7	19.2	31.9	43.6	11.7	43.7	50.4	6.7	25.7	34.6	8.9
34	11.0	28.4	17.4	10.0	26.0	16.0	7.9	29.1	21.2	6.9	22.2	15.3
36	22.3	30.1	7.8	24.1	31.5	7.4	24.1	28.7	4.6	24.1	27.3	3.2
37	24.0	32.0	8.0	26.1	33.4	7.3	24.6	28.5	3.9	22.7	28.2	5.5
40	16.8	26.3	9.5	17.2	29.8	12.6	11.9	30.2	18.3	9.8	18.2	8.4
42	17.4	25.0	7.6	17.8	23.0	5.2	4.3	19.7	15.4	21.7	25.3	3.6
43	11.7	25.8	14.1	14.6	34.8	20.2	17.2	30.4	13.2	20.0	28.6	8.6
45	20.7	30.3	9.6	20.6	27.4	6.8	21.9	36.3	14.4	29.8	36.5	6.7
48	24.8	40.3	15.5	21.5	37.4	15.9	29.9	39.1	9.2	21.2	43.0	21.8
49	31.9	41.7	9.8	31.6	44.8	13.2	25.4*	34.8*	9.4	25.4*	34.8*	9.4
52	31.3	42.0	10.7	35.4	35.7	0.3	34.0	39.9	5.9	32.6	45.1	12.5
53	21.7	30.6	8.9	17.5	31.6	14.1	18.4	30.5	12.1	27.0	33.7	6.7

***Week 1 only, values reflect LOCF (last observation carried forward)**

Comments:

1. No detectable amounts of [redacted] were found in any of the 45 plasma samples analyzed.
2. Dermoval Gel 0.05% clobetasol propionate is used as a comparator drug in these studies. It is noted that this product is not an approved US product. Thus, the data (from Dermoval Gel) may be used as a supportive study only.
3. At inclusion 6 subjects (subjects #5, 15, 36, 42, 44, and 47) did not have normal HPA axis function in terms of an increase of cortisol level of lower than 8 µg/dL after stimulation. Since, these lower values ranging 7.5 to 7.7 µg/dL were close to the inclusion criterion of 8 µg/dL, the Sponsor decided to include these subjects.

4. The results (Tables 1-4) show that all the 52 patients in the Clobetasol Propionate Shampoo and Dermoval Gel group met the pre-specified criteria representative of normal response, i.e., baseline pre-stimulation serum cortisol level ≥ 10 µg/dL, and post-stimulation serum cortisol level of ≥18 µg/dL. However, the study design in general was flawed because of the following reasons:
   - Many subjects exhibited very high levels (> 18 µg/dL) of cortisol at the screening. A doubling of the cortisol levels post-stimulation following Cosyntropin administration would have been unrealistic in these subjects. Thus, these subjects should not have been enrolled in the study.
   - The study subjects were evaluated weekly with Cosyntropin stimulation on weeks 1, 2, 3 and 4. Such frequent exposure with Cosyntropin is likely to manifest higher plasma cortisol levels at the end of the desired 4-week period leading to a false negative interpretation (i.e., no HPA axis suppression).
5. In the seborrheic dermatitis group, at the end of 2-week treatment with Clobex Shampoo, none of the 14 subjects showed post-simulation doubling of the basal plasma cortisol value, and 6 (43%) showed post-stimulation values 1.5-1.8-times higher than their corresponding pre-stimulation value. Additionally, one subject has post-stimulation value of <5 µg/dL.
6. In the seborrheic dermatitis group, at the end of 4-week treatment, only 2 of the 14 subjects (14%) showed post-simulation doubling of the basal plasma cortisol value and 4 (28%) showed post-stimulation values 1.5-1.8-times higher than their corresponding pre-stimulation values.
7. In the psoriasis group, at the end of 2-week treatment with Clobex Shampoo, 6 of the 14 subjects (42%) showed post-simulation doubling of the basal plasma cortisol value and 1 (7%) showed post-stimulation values1.8-times higher than its corresponding basal value. Additionally, one subject has post-stimulation value of <5 ng/dL. Where as at the end of 4-week treatment, only 2 of the 14 subjects (14%) showed post-simulation doubling of the basal plasma cortisol value and 3 (21%) showed post-stimulation values 1.5-1.8-times higher than their corresponding basal values.
8. Since the firm has used the 60-minute test period, the criterion for a normal response is an approximate doubling of the basal plasma cortisol value (Cortrosyn for Injection labeling). Thus, at least 90% (12 out of 13) in the seborrheic dermatitis and 87% (12 out of 14) subjects in the scalp psoriasis group exhibit HPA axis suppression by this criterion.

6.2.4. HPA Axis Suppression Study: Report 2. RD.06.SRE.18070: HPA Axis Suppression Potential of a Clobetasol Propionate Shampoo, 0.05% An Open-Label Study in Adolescents with Scalp Psoriasis.

Objectives:
To evaluate the potential of Clobetasol Propionate Shampoo, 0.05% to suppress the hypothalamus-pituitary-adrenal (HPA) axis in adolescents subjects between 12 to 17 years of age, with moderate to severe scalp psoriasis.

Study Sites: Multi-center, all in the USA (details in Vol. 19, Item 6, page 1652).
Investigational Product: Clobetasol Propionate 0.05% Shampoo, Lot No. PLG-1 (corresponding formulation code: 662.066/BLJ-1).
Dosage Regimen: Once daily topically to a dry scalp (waiting for 15 minutes before lathering and rinsing). Subjects were provided with one 120-g bottle of Clobetasol Propionate Shampoo, 0.05%, at Baseline and one 120-g bottle at Week 2. Each 120 g bottle was supposed to last for 2 weeks during the treatment period.

Duration of Treatment: 4 weeks.
Methods: The study was conducted at three study sites, open-label involving 13 subjects (3 males and 10 females, 10 Whites, 1 Black and 2 Hispanics, ages 12 to 17 years, mean age 14.2 ± 1.91 years). All subjects had a confirmed diagnosis of stable, moderate to severe scalp psoriasis as specified in the entry criteria, with involvement of at least 25% of the scalp. Subjects were also required to have a normally functioning HPA axis defined as a pre-stimulation serum cortisol level of at least 7 µg/dL and a demonstrated response to adrenal stimulation defined as a post-stimulation cortisol level of at least 18 µg/dL approximately 60 minutes after receiving 0.25 mg of cosyntropin via direct intravenous injection (detail criteria described in NDA 21-644, Vol. 1.19 page 1655, 1661-1662).

Qualified subjects received clobetasol propionate shampoo, 0.05% applied once daily to the affected areas of the dry scalp (waiting 15 minutes before lathering and rising) for a period of 4 weeks with a 2-week treatment-free follow-up period. HPA axis function was measured at Screening and at Week 4. Subjects with HPA axis suppression at the end of the treatment period were to be re-tested weekly after the last dose and followed clinically until normal cortisol levels (both a pre-stimulation cortisol level or at lest 7 µg/dL and a post-stimulation level of at least 18 µg/dL were observed. Plasma clobetasol levels were assessed at Week 4 to provide data on systemic exposure.

All 13 subjects completed the study. However, one subject (#20) was found to be a protocol violator for missing 8 consecutive doses (date of first dose Dec 06, 2001, date of last dose Jan 04, 2002, dates dose missed Dec 24 to Dec 31, 2001); and was therefore, excluded from the per protocol population data analysis.

The average weekly Clobetasol Propionate Shampoo used was 22.7 g (S.D. 17.2 , median 14.0 g, range: min — to max ——).
No dermatological adverse effects or other significant drug-related AEs occurred during the study.

Table 5. Report SPR 18070: Pre and Post-Stimulation Cortisol Levels: Clobetasol Propionate 0.05% Shampoo Treatment Group in Seborrheic Dermatitis

	Plasma Cortisol levels (µg/dL)									
	Screening					Week 4				
	Age/Gender	Pre-Stim	Post-Stim	Diff (post-pre)	X-Pre-Stim (Computed)	Pre-Stim	Post-Stim	Diff (post-pre)	X-Pre-Stim (Computed)	HPA Suppression
1	12/F	17.3	24.4	7.1	1.4	19.2	32.6	13.4	1.7	Yes
2	12/F	11.0	40.0	13.1	3.6	18.8	29.0	10.2	1.5	Yes
3	14/F	14.8	34.9	20.1	2.4	27.7	35.7	8.0	1.3	Yes
4	17/M	9.5	30.9	21.4	3.3	16.9	32.3	15.4	1.9	No
5	14/M	11.8	29.5	17.7	2.5	14.4	19.1	4.7	1.1	Yes
6	13/F	16.9	28.8	11.9	1.7	12.3	10.4	-1.9	0.8	Yes
7	15/F	15.0	26.5	11.5	1.8	16.2	35.3	19.1	2.2	No
8	17/M	9.2	28.9	19.7	3.0	7.8	32.4	24.6	4.2	No
9	14/F	19.6	33.6	14.0	1.7	11.4	32.4	21.0	2.8	No
10	12/F	8.7	25.1	16.4	2.9	13.0	29.0	16.0	2.2	No
11	16/F	11.0	33.2	22.2	3.0	7.5	42.0	34.5	5.6	No
19	16/F	11.2	39.3	28.1	3.5	13.6	35.8	22.2	2.6	No
20	12/F	7.4	25.2	17.8	3.4	8.2	23.8	15.6	2.9	No?*

Subject (#20) was found to be a protocol violator for missing 8 consecutive doses, date of first dose ——— date of last dose ——— dates dose missed ——— and was therefore, excluded d by the reviewer from *the per protocol population data analysis.*

Comments:

1. No detectable amounts of [redacted] were found in any of the 11 plasma samples analyzed.
2. Of the 13 subjects enrolled, at least three (subjects #1, 6 and 9) showed the post-stimulation cortisol values at screening less than 2-times (1.4-, 1.7- and 1.7-times, respectively) compared to the respective pre-stimulation values. Thus, inclusion of these subjects in the study is questionable.
3. Subject (#20) was found to be a protocol violator for missing 8 consecutive doses — date of first dose Dec 06, 2001, date of last dose Jan 04, 2002, dates dose missed Dec 24 to Dec 31, 2001—, and was therefore, excluded d by the reviewer from the per protocol population data analysis. Thus, the final interpretation of HPA axis suppression results was based on 12 subjects.
4. Since the firm has used the 60-minute test period, the criterion for a normal response is an approximate doubling of the basal plasma cortisol value (Cortrosyn for Injection labeling). For computation purpose, this reviewer considered post-stimulation/pre-stimulation value ≥ 1.8 as an approximate doubling of the basal cortisol value. With respect to the HPA axis function, at the end of 4 weeks assay, 5 out of 12 subjects (or 42%) have 60-minute post-stimulation cortisol value less than twice those of the corresponding pre-stimulation levels. Per the Cortrosyn labeling criteria, these subjects were considered suppressed.

6.3. OVERALL COMMENTS ON HPA AXIS FUNCTION

Based on the reported results, there appears to be a marked incidence of HPA axis suppression with the Clobex Propionate Shampoo in both the adult and adolescent populations after 4 weeks of topical scalp application. The observed degree of HPA suppression with Clobex Shampoo is sufficient to cause concern about patient's safety in an uncontrolled administration setting.

6.4. RECOMMENDATIONS

From a Biopharmaceutics perspective the firm has provided evidence of systemic availability of the test Clobex Propionate Shampoo using HPA suppression as a pharmacodynamic end point. The Study No. SRE2610 conducted in Europe in adult patients is flawed, and no meaningful results can be interpreted from it. Based on the results of HPA axis trial in adolescents (12-17 years, Study No. SRE 18070), use of Clobex Shampoo is clearly associated with a significant incidence of HPA suppression as 5 out of 12 (42%) evaluable subjects exhibit HPA axis suppression in this population. It is also noted that the number of subjects (N=13) used in Study 18070 was rather small for this type of study. While the bioavailability of clobetasol has been determined via indirect methods (i.e., HPA axis testing), from a clinical pharmacology perspective, the safety issues raised by the suppression of the HPA axis in adolescents brings up a significant concern regarding the adult population that needs to be addressed by the Sponsor. The reviewer, therefore, recommends that the Sponsor conducts HPA axis studies using an appropriate study design with adequate number of subjects both in the adult and adolescent populations for comparative safety purpose.

6.5. OCPB FILING REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics

1. *NEW DRUG APPLICATION FILING AND REVIEW FORM*

1.1.1.1.1 General Information About the Submission

	Information		Information
NDA Number	21-644	Brand Name	Clobex Shampoo™ 0.05%
OCPB Division (I, II, III)	DPE III	Generic Name	Clobetasol Propionate, 0.05%
Medical Division		Drug Class	Topical Steroid
OCPB Reviewer	Chandra S. Chaurasia, Ph. D.	Indication(s)	Treatment of moderate to severe forms of [redacted] scalp psoriasis
OCPB Team Leader	E. Dennis Bashaw, Pharm. D.	Dosage Form	Shampoo
		Dosing Regimen	Once daily to affected area of the scalp. The product should be applied on dry scalp and left in place for 15 minutes before lathering and rinsing. Treatment should be limited to 4 consecutive weeks.
Date of Submission	May 06, 2003	Route of Administration	Topical
Estimated Due Date of OCPB Review	October 15, 2003	Sponsor	Galderma Laboratories, L. P. Fort Worth, TX 76177
PDUFA Due Date	March 05, 2004	Priority Classification	
Relevant IND	IND 60.934		
1.1.1.2 Division Due Date			

1.1.1.2.1.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				**1.1.1.3**
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

Healthy Volunteers-				
single dose:	X	1		Vasoconstriction Assay: CG.03.SRE.2618: Comparing Clobetasol Propionate Shampoo with three commercialized products and its vehicle.
multiple dose:				
Patients-				
single dose:				
multiple dose:		2		HPA Axis Suppression Studies: 1.CG.03.SRE.2620: Ocular Safety and HPA axis suppression study- on both scalp psoriasis and scalp seborrheic dermatitis subjects. 2. RD.06.SRE.18070: HPA axis suppression study in adolescents 12-17 years with scalp psoriasis.
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				**1.1.1.4**
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X			Pooled Data
pediatrics:	X			In Adolescents Age Group 12-17-yr only for HPA Suppression study
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	2		HPA Axis Suppression Studies: 1.CG.03.SRE.2620: Ocular Safety and HPA axis suppression study- on both scalp psoriasis and scalp seborrheic dermatitis subjects. 2. RD.06.SRE.18070: HPA axis suppression study in adolescents 12-17 years with scalp psoriasis.
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				

Alternate formulation as reference:				
Bioequivalence studies -				
Traditional design; single / multi dose:				
Replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		Three in vivo and one in vitro studies
1.1.1.4.1.1				

1.1.1.4.1.2 Filability and QBR comments

1.1.1.5	**"X" if yes**	1.1.1.5.1.1.1.1.1 Comments
1.1.1.6 Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
1.1.1.7 Comments sent to firm		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• ***What are the highlights of the physicochemical properties of clobetasol propionate?*** • ***What are the properties of the formulation of the drug product? What are the differences between clinical and to-be-marked formulations?*** • *What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of clobetasol propionate?* • *What studies have been conducted for biopharmaceutic/bioavailability evaluation of the drug product? What are the outcomes of these studies?* • *Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters?* • What are the basic pharmacokinetic parameters of clobetasol propionate (ADME)? • Is the vasoconstriction assay appropriate to classify the potency class of clobetasol propionate shampoo? What are the outcomes of this study? • Is the study to evaluate clobetasol propionate shampoo potential to suppress the hypothalamus-pituitary-adrenal (HPA) axis appropriately designed with respect to the study populations relevant to the proposed indication? • Are there any differences between clinical and to-be-marketed formulations? • Are there any in vitro data for clobetasol propionate shampoo formulation? • What bioanalytical methods are used to assess the amount of clobetasol in plasma and for in vitro analyses? • Are analytical methods sensitive enough to determine the extent of clobetasol propionate absorption after topical application?	

Other comments or information not included above	The Sponsor has submitted 4 Phase II and 5 phase III pivotal controlled studies (including 3 Supportive European studies) for the clinical evaluation of the test product in scalp psoriasis and scalp seborrheic dermatitis patients. No traditional in vivo pharmacokinetic studies have been submitted. The submission of HPA and other dynamic studies are acceptable for the assessment of in vivo pharmacokinetics in the situation where in vivo pk studies are not possible.
Primary reviewer Signature and Date	**Chandra S. Chaurasia, Ph. D.**
Secondary reviewer Signature and Date	**E. Dennis Bashaw, Pharm. D.**

CC: NDA 21-644, HFD-850 (P. Lee), HFD-540 (J. Smith), HFD-880 (D. Bashaw, J. Lazor, A. Selen)

End of Document

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chandra S. Chaurasia
1/7/04 05:00:58 PM
BIOPHARMACEUTICS

Thanks again.

Dennis Bashaw
1/7/04 05:18:27 PM
BIOPHARMACEUTICS